METHOD FOR ASSESSING BEHAVIORAL PREDISPOSITION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 60/486,640 filed Jul. 11, 2003. This application is incorporated herein by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] The present invention was made with US Government funding provided by National Institutes of Health, National Institute of Mental Health, Grant Nos. MH 49414 and MH 45070. The United States Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] A decades long search for conclusive evidence of interplay between genotype and environment to yield a behavioral effect has not succeeded. It has long been postulated that such interplay will exist, but these have not been demonstrated prior to the invention described herein. See Rutter, M. and J. Silberg, "Gene-Environment Interplay in Relation to Emotional and Behavioral Disturbance,"*Ann. Rev. Psychol.* 53:463-490 (2002). Demonstration of such an effect would be of great interest to psychiatrists, psychologists, social workers, law enforcement and justice administration personnel, and others involved with behavioral issues.

[0004] The invention described in this application relates, in part, to an interaction between a pathogenic environmental risk factor (childhood maltreatment) and a genotype (allelic profile at a genetic locus that encodes monoamine oxidase A [MAOA]). Childhood maltreatment is a universal risk factor for antisocial behavior. Boys who experience abuse—and more generally, those exposed to erratic, coercive, and punitive parenting—are at risk of developing conduct disorder, evidencing antisocial personality symptoms, and of becoming violent offenders. The earlier children experience maltreatment, the more likely they are to develop these problems. But there are large differences among children in their response to maltreatment. Although maltreatment increases the risk of later criminality by about 50%, most maltreated children do not become delinquents or adult criminals. The reason for this variability in response is largely unknown, but it may be that vulnerability to adversities is conditional upon genetic susceptibility factors.

[0005] The MAOA gene, located on the X chromosome (Xp11.23-11.4), encodes the MAOA enzyme, which metabolizes, and renders inactive, neurotransmitters such as norepinephrine (NE), serotonin (5-HT) and dopamine (DA). Genetic deficiencies in MAOA activity have been linked with aggression in mouse and man. Increased aggression, and increased levels of brain NE, 5-HT, and DA, were observed in a transgenic mouse line in which the gene encoding MAOA was deleted, and aggression was normalized by restoring MAOA expression. In humans, a null allele at the MAOA locus was linked with male antisocial behavior in a Dutch kindred. Because MAOA is an X-linked gene, affected males with a single copy produced no MAOA enzyme—effectively, a human knockout. However, this mutation is extremely rare. Evidence for an association between MAOA and aggressive behavior in the human general population remains inconclusive.

[0006] Animal studies document that maltreatment stress (e.g., maternal deprivation, peer rearing) in early life alters NE, 5-HT, and DA neurotransmitter systems in ways that can persist into adulthood and influence aggressive behaviors. In humans, altered NE and 5-HT activity are linked to aggressive behavior. Maltreatment has lasting neurochemical correlates in human children. Deficient MAOA activity may dispose the organism toward neural hyper-reactivity to threat, as evidenced by the inhibitory action of phenelzine injections which inhibit the action of monoamine oxidase and prevented rats from habituating to chronic stress. Low MAOA activity may be particularly problematic early in life, because there is insufficient MAOB (a homolog of MAOA with broad specificity to neurotransmitter amines) to compensate for an MAOA deficiency.

[0007] In a related aspect, the invention relates in part to an interaction between a second pathogenic environmental risk factor (life stress) and a second genotype (allelic profile at a genetic locus that encodes 5-HTT), where the second genotype is conditionally associated with depression and the second environmental risk factor conditionally moderates the association.

[0008] Depression is among the top five leading causes of disability and disease burden throughout the world. Across the life span, stressful life events that involve threat, loss, humiliation, or defeat influence the onset and course of depression. But not all people who encounter a stressful life experience succumb to its depressogenic effect. Diathesis-stress theories of depression predict that individuals' sensitivity to stressful events depends on their genetic makeup. Behavioral genetics research supports this prediction, documenting that the risk of depression following a stressful event is elevated among people who are at high genetic risk and diminished among those at low genetic risk. But whether specific genes exacerbate or buffer the effect of stressful life events on depression is unknown.

[0009] The serotonin system is the target of selective serotonin re-uptake inhibitor drugs that are effective in treating depression. The serotonin transporter has received particular attention because it is involved in the re-uptake of serotonin at brain synapses. The promoter activity of the 5-HTT gene, located on 17q11.2, is modified by polymorphic sequence elements within the proximal 5' regulatory region, designated the 5-HTT gene-linked polymorphic region (5-HTTLPR). A short ('s') allele in the 5-HTTLPR is associated with lower transcriptional efficiency of the promoter than is a long ('l') allele.

[0010] Evidence for an association between the short promoter variant and depression is inconclusive. Although the 5-HTT gene may not be directly associated with depression, it could moderate the serotonergic response to stress, for several reasons. First, in mice with disrupted 5-HTT, homozygous and heterozygous (5HTT −/−, +/−) strains exhibit more fearful behavior and greater increases in the stress hormone adrenocorticotropin (plasma ACTH) in response to stress compared to homozygous (5HTT +/+) controls, but in the absence of stress no differences related to genotype are observed. Second, in rhesus macaques, whose length variation of the 5-HTTLPR is analogous to